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Letter to the Editor

Comparison of Female and Male Interstitial Deletions in the Distal Xq

To the Editor:

We reviewed female interstitial deletions in the distal Xq and compared them to those reported in males [Schmidt, 1996]. Most of the deletions were common to females and males, and they were scattered within Xq27 and proximal Xq. Six females had large deletions of 1–10 Mb which formed a contig covering ~13 Mb within Xq27.1→proximal Xq28 (Fig. 1). In 3 of these patients the deleted X chromosome was preferentially active, and the phenotype was abnormal (mental retardation in the patient of Schmidt et al. [1990]; mental retardation and Hunter syndrome in the patient of Clarke et al. [1992]; and mental retardation and myotubular myopathy in the patient of Dahl et al. [1995]). All three deletions occurred de novo. Our previous analysis of these deletions showed no abnormalities in the methylation and replication patterns of the region distal to the deletion, and in the corresponding area on the normal X chromosome [Schmidt et al., 1994]. Thus, there is no evidence that the skewed inactivation pattern in these cases resulted from the cell selection driven by anomalies of X inactivation.

Three other large deletions, and three overlapping small ones, were found in normal females. All of these were detected because of the affected male offspring to whom the deleted X chromosome had been passed. The boys were all mentally retarded, and one additionally had Hunter syndrome. In each of the carrier mothers the X inactivation pattern was random. This finding is remarkable, as the area covered by these deletions (~12 Mb) almost fully overlaps with that of the three deletions with skewed inactivation pattern. We conclude that deletions of Xq27→proximal Xq28 do not promote cell selection against the deleted X chromosome as active. The resulting inactivation pattern is established by chance. The above conclusion is supported by two other female deletions of Xq27 presented by Willard [1996]. This implies that phenotypically normal carriers may have affected daughters if the deleted X chromosome in the offspring is preferentially active.

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Address reprint requests to Malgorzata Schmidt, Department of Genetics and Human Variation, La Trobe University, Melbourne 3083, Australia.

It has been known that females with deletions of the terminal Xq are fertile [Skibsted et al., 1984; Tharapel et al., 1993]. Our comparison of female and male deletions confirms that breakpoints within Xq27.1→proximal Xq28 do not interfere with female fertility, since the deletions of Quan et al. [1995], Meijer et al. [1994], Gedeon et al. [1992, 1995], and Beck et al. [1992] were all passed to the offspring (Fig. 1). While it is too early to exclude premature ovarian failure in the carriers of these deletions, there is no clear evidence for it. In the case of Quan et al. [1995] the mother was 33, in the family of Meijer et al. [1994] 4 carriers had 3 or 2 children each (ages 19, 17, and 9 in one case), and in the family of Gedeon et al. [1992] 1 carrier had 3 children and another had 4, the youngest being 19.

In summary, mental status in females with interstitial deletions of terminal Xq is determined by the pattern of X inactivation, which is highly variable. In contrast, fertility may not be affected at all.

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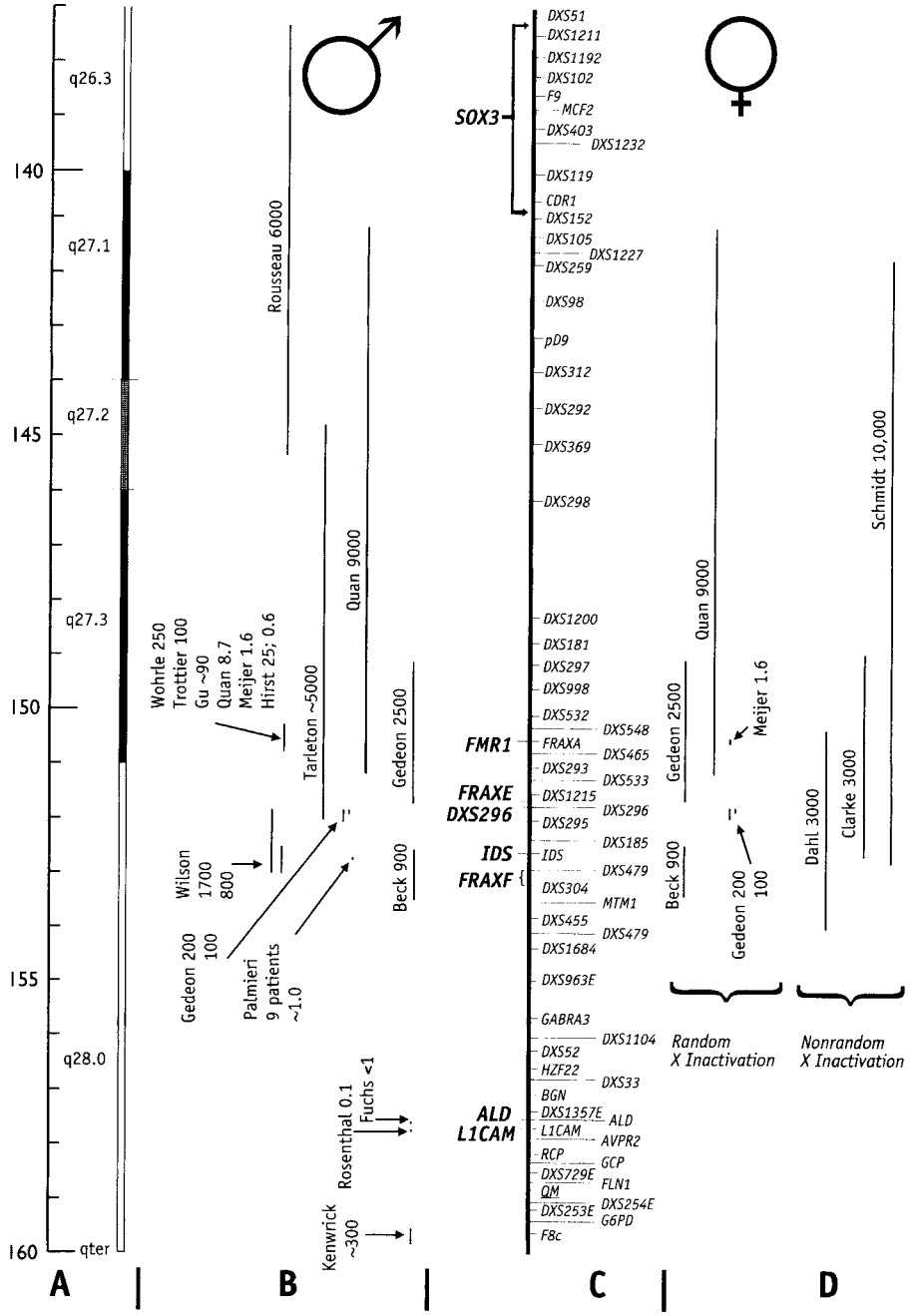

Fig. 1. Male (**left**) and female (**right**) interstitial deletions in the distal Xq. **A**: Map of X chromosome scaled in megabases. **B**: Deletions reported in males are represented by vertical lines with name of first author and approximate size in kb. **C**: Order of X chromosome markers [Willard et al., 1994]. Bold horizontal symbols indicate position of known genes involved in mental retardation. The position of SOX3 [Stevanovic et al., 1993] has been narrowed (Schmidt, unpublished) using an X chromosome with a duplication DXS152 → Xqter Schmidt et al., 1991. **D**: Deletions reported in females are grouped according to X-inactivation pattern (in French brackets). In each of those indicated as having nonrandom X-inactivation, the deleted X was active and the individual was mentally retarded. Name of first author and approximate size of deletion in kb are given. References: Fuchs < 1, Sarde et al., 1994; Gedeon 200, 100, Gedeon et al., 1995; Gedeon 2500, Gedeon et al., 1992; MTM1, Dahl et al., 1995; Schmidt 10,000, Schmidt et al., 1990; SOX3, Stevanovic et al., 1993; Tarleton ~5000, Albright et al., 1994; Wilson 1700, 800, Steen-Bondeson et al., 1992; Wohrle 250–Hirst 25, 0.6, Hirst et al., 1995 (deletions reported by de Graaff et al. [1995] are not included in Fig. 1, as they result from somatic instability of the expanded FMR1 gene).

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Malgorzata Schmidt
Department of Genetics and Human Variation
La Trobe University
Melbourne, Australia